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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,651	12/27/2001	Peter Laurence Molloy	50179-093	9660

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EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Application No.	Applicant(s)	
09/914,651	MOLLOY ET AL.	
Examiner	**Art Unit**	
Gerald G. Leffers Jr., PhD	1636	

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *54-59,61-67,69-85,87-95 and 97-107* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *54-59,61-65,67,69-84 and 107* is/are allowed.

6)☒ Claim(s) *85,87-95 and 97-105* is/are rejected.

7)☒ Claim(s) *66 and 106* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Response to Amendment

Receipt is acknowledged of an amendment, filed on 12/30/2004, in which claims several claims were amended (claims 54, 61-65, 69-73, 79-80, 85, 87-89, 95 and 97-99), a new claim was added (claim 107) and in which a single claim was cancelled (claim 60). Claims 54-59, 61-67, 69-85, 87-95, 97-107 are pending in the instant application.

Any rejection of record in the previous office action not addressed herein is withdrawn. This action is FINAL.

Claim Objections

Claim 66 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 65, upon which claim 66 is dependent, already recites that the PSM enhancer element is operatively linked to a promoter.

Claims 103 & 105 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 95, upon which claims 103 & 105 are dependent, already specifies that the cancer is prostate cancer.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 85, 87-95, 97-105 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) *in vitro* embodiments directed to expression of a desired polypeptide sequence when the polynucleotide sequence is operatively linked to the recited PSMA enhancer element and promoter, and (ii) methods of treating prostate cancer wherein the vector used comprises a recombinant expression cassette comprising a polynucleotide sequence encoding an enzyme that converts a prodrug to a toxic drug operatively linked to both an enhancer element obtained from intron 3 of the PSM gene and a promoter element, does not reasonably provide enablement for any other *in vivo* embodiments wherein the claimed regulatory elements are used to direct expression of a given heterologous sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the action mailed on 9/23/2004, and which are repeated below.**

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of

experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The invention is extraordinarily complex, encompassing the use of novel transcriptional regulatory elements (i.e. enhancer elements obtained from the 3rd intron of the human prostate specific membrane antigen gene) to drive expression of a therapeutic nucleic acid sequence in a given host organism such that efficacious treatment is achieved. The only disclosed utility for *in vivo* embodiments of the claimed invention for which the specification provides any significant guidance at all is for the therapeutic treatment of a disease or condition in a human (e.g. prostate cancer). Thus, the rejected claims read on *in vivo* gene therapy.

Breadth of the claims: The breadth of the claims greatly exacerbates the complexity of the invention. The broadest claims encompass any disease or condition (e.g. any cancer). The claims encompass the use of any gene sequence or antisense sequence to achieve a therapeutic effect when operatively linked to the prostate-specific enhancer element of the invention.

Guidance of the specification/The existence of working examples: The specification teaches the isolation and characterization of an ~2.5 kb enhancer region obtained from the 3rd intron of the PMSA gene (e.g. Examples 1-3 of the instant specification). The working examples teach *in vitro* experiments that demonstrate multiple constructs obtained from the 3rd intron of the PMSA gene can enhance the tissue-specific expression of operatively-linked nucleic acid sequences when linked to different promoter elements (e.g. probasin promoter, prostate specific antigen gene promoter (i.e. the PSA promoter), herpes simplex virus thymidine kinase promoter (i.e. the TK promoter), etc.; e.g. Example 7, Figure 9a). In general, the tissue specificity

observed for the different enhancer elements mirrors the expression data for the PSMA gene in different cell types, with by far the greatest level of enhancement activity observed in prostate cell types such as LN3 or PC3 (e.g. Examples 4-7 & 10, Figure 7). This strong tissue-specificity for prostate cell types was maintained when the enhancer elements were presented as part of an ovine atadenoviral backbone (e.g. Example 12, Figure 12). Although the specification speculates that the level of expression seen in the kidney cell line tested (i.e. HEK293 cells) might be biologically meaningful since PSMA is expressed at low levels in proximal kidney tubules, the level of enhancement of expression is low relative to prostate cell lines (e.g. Figures 9a & 9b). A single working example is provided concerning enhancement of expression activity in human umbilical artery cells (HUAECs) or vein cells (HUVECs) since PSMA is known to be expressed in the neovasculature of several tumor types, but not in normal vasculature (e.g. Example 13). While it is stated that an enhancer element of the invention did result in some degree of neovasculature-specific enhancement of operatively-linked reporter sequences in the HUAEC and HUVEC cells, the level of enhancement is not indicated.

While the specification asserts other *in vivo* utilities for the claimed methods of expressing a gene operatively linked to the enhancer elements of the invention (e.g. providing a target for the development of agents that may interfere with gene expression in the target cell types-page 4, last paragraph), no significant guidance is provided for any of these asserted utilities. No working examples are provided, for example, where a given "therapeutic gene" is operatively linked to an enhancer element of the invention and efficacious expression is observed in an animal model for a given disease (e.g. a given type of cancer).

State of the art/Predictability of the art: The prior art appears to be silent with regard to the use of the specific enhancer elements taught in the instant specification. Thus, the prior art does not offset the deficiencies of the instant specification with regard to enabling the full, broadly claimed scope of the invention.

In general, gene therapy is a highly unpredictable and undeveloped field and the skill in the art is high. See Orkin et al (U) which states (page 1):

2. While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA Advisory Committee (RAC)-approved protocols.

3. Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host.

The consensus scientific opinion is that gene therapy was and still is highly unpredictable as evidenced by Orkin et al. The teachings of Verma et al (V), two years after the Orkin et al publication, reaffirm the teachings of Orkin et al that, even after the two years, there is no evidence of how to use gene therapy to predictably to treat any disease. Verma et al teach "Although more than 200 clinical trials are currently underway worldwide, with hundreds of patients enrolled, there is still no single outcome that we can point to as a success story." (Page 239, column 1). This reference teaches the considerable hurdles that must be overcome, including making sure that delivery of the gene gets to the right cells and getting enough of the gene delivered (page 239). This reference teaches that "The Achilles heel of gene therapy is

gene delivery....Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression. Most of these approaches suffer from poor efficiency of delivery and transient expression of the gene." (page 236, column 3). Palù et al (J. Biotechnol. (1999) 68: 1-13) teaches that despite hundreds of clinical trials underway, no successful outcome has been achieved (Palù et al, p. 1, Abstract). The continued, major obstacles to successful gene therapy are gene delivery and sustained expression of the gene. Regarding non-viral methods for gene delivery, Verma et al indicates that most approaches suffer from poor efficiency and transient expression of the gene (p. 239, col. 3, 2nd paragraph). Likewise, Luo et al (Nature Biotechnology (2000) 18:33-37) indicates that non-viral synthetic delivery systems are very inefficient (e.g. see p. 33, Abstract and col. 1, 1st and 2nd paragraphs).

Although the references cited above indicate the promise of gene therapy, it is still a technique of the future and advancements in our understanding of the basics of gene delivery and expression must be made before gene therapy becomes a useful technique. As recently as April of 1998 French Anderson (W) reviewed the status of the field of gene therapy and concluded that "Except for anecdotal reports of individual patients being helped, there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease." (page 25, column 1). More recently, the most advanced clinical trial for the gene therapy treatment of severe combined immunodeficiency disease (SCID), the only disease for which has purportedly been "cured" by gene therapy, has been halted due to the development of cancer in two of the subjects. In both cases the retrovirus used to deliver the corrective gene to the patient inserted itself into a stretch of a gene associated with childhood leukemia (Nature, February 2003, Vol. 421, page 678, "Cancer fears cast doubts on future of gene therapy").

The amount of experimentation necessary: Given the factors outlined above, especially with regard to the high state of the art required to practice gene therapy, and the unpredictability of the art with regard to gene therapy in general, it would have required undue, unpredictable experimentation to practice the claimed invention in the full, broadly claimed scope encompassed by the rejected claims.

Response to Arguments

Applicant's arguments filed 12/30/2004 in response to similar grounds of rejection made in the previous office action have been fully considered but they are not completely persuasive. The response traverses the rejection as it applies to the amended claims for reasons already of record and essentially argues that the amendment of the claims has obviated the outstanding grounds of rejection (claim 85 has been amended to recite a method of directing expression in a prostate cell; claim 95 has been amended to recite a method of treating prostate cancer).

To the extent that the rebuttal arguments presented by the examiner in the previous office action are still applicable, they are incorporated here by reference. Applicants' response completely ignores the portion of the rejection directed to the type of heterologous nucleic acid that is operatively linked to the PSM enhancer element (i.e. "polynucleotide sequence encoding an enzyme that converts a prodrug to a toxic drug operatively linked to both an enhancer element obtained from intron 3 of the PSM gene and a promoter element"). There is no significant guidance anywhere in the specification concerning the use of other coding sequences to therapeutic effect. As stated previously, there is also no significant guidance with regard to any other broadly asserted *in vivo* utilities for the claimed methods (i.e. claim 85 and dependent claims). For reasons of record, the claims remain rejected as not being enabled for embodiments

where the heterologous nucleic acid sequence that is operatively linked to the prostate specific enhancer of the invention encodes a protein other than an enzyme that converts a prodrug to a toxic compound.

Conclusion

Claims 54-59, 61-67, 69-85, 87-95, 97-107 are pending in the instant application. Claims 54-59, 61-65, 67, 69-84 & 107 are allowed. Claims 85, 87-95, 97-105 are rejected. Claims 66, 103 & 105 are objected as failing to further limit the claims upon which they depend. Claim 106 is objected to as being dependent upon a rejected claim, but would be allowable if rewritten in independent form comprising each of the limitations of the claim upon which it is currently dependent.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G. Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

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